Stage-specific regulation of reprogramming to induced pluripotent stem cells by wnt signaling and T cell factor proteins.

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Public Summary:
Reprogramming of differentiated cells to induced pluripotent stem cells is a step-wise process of transcriptional changes. Here, we demonstrate that reprogramming signals can be biphasic, using the Wnt pathway as an example. The data point to opposing effects of Wnt signaling and its downstream regulators, the Tcf proteins, early and late in the reprogramming process, indicating that events promoting one phase can be inhibitory for a subsequent phase. These observations should encourage the development of dynamic reprogramming approaches.

Scientific Abstract:
Wnt signaling is intrinsic to mouse embryonic stem cell self-renewal. Therefore, it is surprising that reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) is not strongly enhanced by Wnt signaling. Here, we demonstrate that active Wnt signaling inhibits the early stage of reprogramming to iPSCs, whereas it is required and even stimulating during the late stage. Mechanistically, this biphasic effect of Wnt signaling is accompanied by a change in the requirement of all four of its transcriptional effectors: T cell factor 1 (Tcf1), Lef1, Tcf3, and Tcf4. For example, Tcf3 and Tcf4 are stimulatory early but inhibitory late in the reprogramming process. Accordingly, ectopic expression of Tcf3 early in reprogramming combined with its loss of function late enables efficient reprogramming in the absence of ectopic Sox2. Together, our data indicate that the stepwise process of reprogramming to iPSCs is critically dependent on the stage-specific control and action of all four Tcfs and Wnt signaling.